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### TREATMENT SATISFACTION INSTRUMENTS FOR DIFFERENT PURPOSES DURING A PRODUCT'S LIFECYCLE—KEEPING THE END IN MIND

Rofail D[1], Regnault A[2], Taylor F[1], Filonenko A[3]
[1]Mapi Values Ltd, Bollington, Cheshire, UK; [2]Mapi Values, Lyon, France; [3]Bayer Schering Pharma AG, Berlin, Germany

**OBJECTIVES:** There are three main parts during a product's lifecycle when satisfaction instruments are particularly useful. These are to aid: 1) getting the product to the market; 2) getting the market to the product; and 3) demonstrating value for health care practitioners during daily clinical practice. This study investigates whether the development and implementation of treatment satisfaction instruments during a product's lifecycle are informed by their purpose. **METHODS:** A literature review was performed between 2000 and 2010 using electronic databases (PUBMED, PsycINFO, and EMBASE) and keywords such as "satisfaction" and "medication" or "drug" and "questionnaire." Relevant articles were reviewed in detail to extract information regarding the satisfaction instrument used, its development and validation, and when the instrument was used during a product's lifecycle. Additional information was collated including the type of studies the instruments were used in, clinical condition/indication, type of data generated (e.g. descriptive), and whether satisfaction was associated with other endpoints. **RESULTS:** Of 875 abstracts, 105 articles were further considered. The review indicated similarities regarding the development and validation of satisfaction instruments, such as using patient input to derive the items and exploring classical measurement properties specific to the target population. However, the specificities of the implementation of treatment satisfaction during the three main stages of a product's lifecycle were rarely considered. **CONCLUSIONS:** The development and implementation of treatment satisfaction instruments during a product's lifecycle rarely consider the purpose. By "keeping the end in mind," data from treatment satisfaction instruments can help three key parts: 1) getting the product to the market thus helping to generate evidence as part of an overall value proposition; 2) getting the market to the product; and 3) demonstrating the value to clinical practice. Furthermore, the development, validation and interpretation of scores from treatment satisfaction instruments should be sensitive to the intended purpose.

## CONCEPTUAL PAPERS & RESEARCH ON METHODS – Statistical Methods

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### SYSTEMATIC REVIEW OF METHODS FOR META-ANALYSIS AND INDIRECT COMPARISON USED IN EXISTING SYSTEMATIC REVIEWS AND HTA REPORTS—RESULTS FROM THE FIRST PART OF EBAYESMET PROJECT

Walczak J[1], Borowiack E[1], Kowalska M[1], Nikodem M[2], Zapalska A[1]
[1]Arcana Institute, Cracow, Poland; [2]CASPolska, Myslenice, Poland

**OBJECTIVES:** To collect information serve as a background for further activities of the eBayesMet project. To perform assessment of the frequency of use the particular statistical methods for meta-analyses and indirect comparisons in existing systematic reviews and HTA reports. **METHODS:** Database of Reviews of Effectiveness (DARE) was searched for relevant reviews published between January 2009 and March 2010. **RESULTS:** The majority of meta-analyses were prepared by using direct statistical methods (97%). The most popular expression about fixed model was that fixed effect model with the Mantel-Haenszel was used (36%). In case of random model, information that method DerSimonian Laird was selected (38%) was used most often. Meta-analyses were prepared mostly based on randomized controlled trials (87%) and in 3% only on observational studies. In meta-analyses based on RCTs in 42% of cases authors mentioned that to make strong conclusion more studies were needed. Employing Bayesian methods was generally very rare. For indirect comparisons six methods were recognized and the most common type was MTC Bayesian Model (53%). Observational studies were not included in any identified analysis. In 40% of the review information indicating the need for additional studies was contained. **CONCLUSIONS:** Our systematic reviews demonstrates a wide range of approaches and methods for conducting meta-analyses and indirect comparison used in current practice. The most popular approach for indirect comparison is Bayesian included network and MTC (over 65%). However performed analysis indicated that Bayesian approach is still marginal methods for performing direct comparison based on head to head studies. Bayesian models have essential advantage: some additional data can be included (as a prior distribution). This extra information can be for instance data from observational studies. However it should be emphasized, that in the analyzed random sample of systematic reviews studies other than RCT were included in only 13%.

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### IMPROVED SURVIVAL CURVE FITS TO SUMMARY DATA FOR ECONOMIC EVALUATIONS

Hoyle MW
University of Exeter, Exeter, UK

**OBJECTIVES:** Estimates of mean cost and quality-adjusted-life-years are central to the cost-effectiveness analysis of health technologies. They are often calculated from curve fits to overall survival and time on treatment, ideally by the method of maximum likelihood applied to individual patient data. However, such data is often not available. Instead, curves are commonly fit to summary Kaplan-Meier estimators, either by regression of the transformed estimator or by minimizing the sums of squares of differences between actual and fitted values. However, the tail of the estimator is often uncertain due to small numbers of patients at risk, and the curve fits do not yield estimates of the true uncertainty in survival times, which is a very important component of overall uncertainty in cost-effectiveness. Here, I describe a new, more accurate method of fitting survival curves to summary survival data. **METHODS:** First, I estimate the underlying individual patient data from the Kaplan-Meier estimator, numbers of patients at risk and from other published trial-related information. The fitted curve is then estimated by maximum likelihood given the estimated underlying individual patient data. **RESULTS:** Simulation applied to individual patient data shows that the method tends to give a more accurate curve fit than the traditional methods of fitting to the Kaplan-Meier estimator. Furthermore, the curve fit is often very similar to that derived by fitting to the underlying individual patient data by maximum likelihood. The method naturally yields accurate estimates of the uncertainty in survival times. When applied to economic evaluations submitted to NICE, the method often yields substantially improved estimates of cost-effectiveness compared to estimates based on fitting survival curves in the traditional manner. This highlights the sensitivity of many cost-effectiveness analyses to curve fits. **CONCLUSIONS:** When only summary survival data is available, I recommend the method for cost-effectiveness analysis.

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### BIAS IS WORSE THAN NOISE: HANDLING MISSING DATA FOR CONFOUNDERS IN OBSERVATIONAL STUDIES

Elkin EP, Exuzides AK, Pasta DJ, Miller DP
ICON Clinical Research, San Francisco, CA, USA

**OBJECTIVES:** Outcomes research often employs observational designs (e.g., disease registries, administrative health care data sets, chart reviews). Researchers using observational data may find various amounts of missing data for confounders when analyzing the association between an exposure (such as treatment use) and an outcome (such as an adverse event). This abstract examines the case when a potentially important confounding variable has a large amount of missing data and compares the analytic methods that may be used in this situation. **METHODS:** Strategies for handling missing confounder information include: (1) ignore confounders with lots of missing values; (2) exclude cases that are missing a confounder value; (3) impute a value for the confounder; (4) include missing as a separate category in the analysis. Data from a disease registry were used as the basis for simulations to compare the odds ratio for risk of death in patients who received a treatment compared to those without treatment. Both a clinical measurement and a subjective physician assessment are known to confound the relationship between treatment and death. **RESULTS:** The most problematic pattern of missing data was informative missing data. In one simulation, the clinical measurement was a strong predictor of death; however, it was disproportionately missing in patients who had died. The physician assessment predicted death strongly among patients missing the clinical measurement, but only weakly in patients not missing the clinical data. Different approaches to the missing confounder data either exacerbated or ameliorated the problem. **CONCLUSIONS:** Excluding cases can create misleading results due to selection bias. Combining all missing values into a separate category can create data "noise" (i.e., classification error); however, this may be the most transparent strategy and least likely to bias results. It is important to include all cases and all potential confounders in the analysis of outcomes research studies.

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### SYSTEMATIC REVIEW OF STATISTICAL METHODS OF META-ANALYSIS AND INDIRECT COMPARISON POTENTIALLY AVAILABLE TO USE IN SYSTEMATIC REVIEWS—RESULTS FROM THE FIRST PART OF EBAYESMET PROJECT

Walczak J[1], Nikodem M[2], Siedmiogrodzki K[2], Zapalska A[1], Borowiack E[1]
[1]Arcana Institute, Cracow, Poland; [2]CASPolska, Myslenice, Poland

**OBJECTIVES:** To collect information serve as a background for further activities of the eBayesMet project. To identify statistical methods and approaches for performing meta-analyses and indirect comparisons. To describe limitations and mathematical background, to discuss advantages and disadvantages of identified methods. **METHODS:** Databases such as MathSciNet, Medline and Cochrane Methodology Group resources, textbooks, guidelines for preparing systematic reviews were searched. We focused on papers with strictly mathematical descriptions of presented methods. **RESULTS:** Eleven main statistical methods were identified. There were six methods of meta-analysis (Inverse Variance, Mantel-Haenszel, DerSimonian-Laird, Peto, Bayesian and Generalized Linear Mixed Models for direct comparison), and five methods of indirect and mixed comparison (Bûcher, Minimal Squares, Lumley, Bayesian Mixed Treatment Comparison and Generalized Linear Mixed Models for indirect comparison). Moreover, there are different variants of some of these methods. For any type of analysis (direct, indirect, network, fixed, random, etc.) and any given data, there is an adequate version of Bayesian method for performing estimation. We found the Bayesian approach to be generally the most flexible.Analysis of precision and credibility of all identified statistical methods of meta-analysis and indirect comparison will be prepared in the next part of eBayesMet project. **CONCLUSIONS:** There are several statistical methods for performing proper data analysis in any model. The problem is with choosing optimal one for the given data set. On the other hand, all methods are less reliable and accurate for samples of data, especially for small (or zero) number of events in one or both arms. There is variety of statistical methods combining direct and indirect evidence, from which the most flexible is Mixed